This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

- 1. (canceled).
- 2. (canceled).
- 3. (canceled).
- 4. (canceled).
- 5. (canceled).
- 6. (canceled).
- 7. (canceled).
- 8. (canceled).
- 9. (canceled).
- 10. (canceled).
- 12. (canceled).
- 13. (canceled).
- 14. (canceled).
- 15. (canceled).
- 16. (canceled).
- 17. (canceled).
- 18. (canceled).
- 19. (canceled).
- 20. (canceled).
- 21. (canceled).
- 22. (canceled).

- 23. (canceled).
- 24. (canceled).
- 25. (canceled).
- 26. (canceled).
- 27. (canceled).
- 28. (canceled).
- 29. (canceled).
- 30. (canceled).
- 31. (canceled).
- 32. (canceled).
- 33. (canceled).
- 34. (canceled).
- 35. (canceled).
- 36. (canceled).
- 37. (canceled).
- 38. (canceled).
- 39. (canceled).
- 40. (canceled).
- 41. (canceled).
- 42. (canceled).
- 43. (canceled).

44. (amended) A method of treating an organism having a disease characterized by the undesired production of a protein comprising contacting the organism with a compound of claim 34 comprising a plurality of units linked by covalent linkages in a sequence that is hybridizable to a complementary nucleic acid, wherein:

said units are selected from nucleosides and nucleobases:

said nucleosides are selected from α-nucleosides, β-nucleosides including 2'deoxy-erythro-pentofuranosyl β-nucleosides, 4'-thionucleosides, and carbocyclic-nucleosides;
said nucleobases are selected from purin-9-yl and pyrimidin-1-yl heterocyclic
bases;

said linkages are selected from charged 3'-5' phosphorous, neutral 3'-5' phosphorous, charged 2'-5' phosphorous, neutral 2'-5' phosphorous or non-phosphorous linkages; and

said sequence of linked units is divided into at least two regions, wherein:

a first of said regions includes said nucleobases linked by nonphosphorous linkages and nucleobases that are attached to phosphate linkages via
non-sugar tethering groups, and nucleosides selected from said α-nucleosides
linked by charged and neutral 3'-5' phosphorous linkages, said α-nucleosides
linked by charged and neutral 2'-5' phosphorous linkages, said α-nucleosides
linked by non-phosphorous linkages, said 4'-thionucleosides linked by charged
and neutral 3'-5' phosphorous linkages, said 4'-thionucleosides linked by charged
and neutral 2'-5' phosphorous linkages, said 4'-thionucleosides linked by nonphosphorous linkages, said carbocyclic-nucleosides linked by charged and neutral

3'-5' phosphorous linkages, said carbocyclic-nucleosides linked by charged and neutral 2'-5' phosphorous linkages, said carbocyclic-nucleosides linked by non-phosphorous linkages, said β-nucleosides linked by charged and neutral 2'-5' linkages, and said β-nucleosides linked by non-phosphorous linkages; and

a second of said regions includes said 2'-deoxy-erythro-pentofuranosyl β-nucleosides linked by charged 3'-5' phosphorous linkages having a negative charge at physiological pH.

- 45. (canceled)
- 46. (canceled)
- 47. (amended) A method of treating an organism having a disease characterized by the undesired production of a protein comprising contacting the organism with a compound of claim 39 comprising a plurality of units linked by covalent linkages in a sequence that is hybridizable to a complementary nucleic acid, wherein:

said units are selected from nucleosides and nucleobases;

said nucleosides are selected from α-nucleosides, β-nucleosides, 4'thionucleosides and carbocyclic-nucleosides;

said nucleobases are selected from purin-9-yl and pyrimidin-1-yl heterocyclic bases;

said linkages are selected from charged phosphorous, neutral phosphorous or nonphosphorous linkages; and

said sequence of linked units is divided into at least two regions, wherein:

a first of said regions includes said α-nucleosides linked by charged and neutral 3'-5' phosphorous linkages, said α-nucleosides linked by charged and neutral 2'-5' phosphorous linkages, said α-nucleosides linked by non-phosphorous linkages, said 4'-thionucleosides linked by charged and neutral 3'-5' phosphorous linkages, said 4'-thionucleosides linked by charged and neutral 2'-5' phosphorous linkages, said 4'-thionucleosides linked by non-phosphorous linkages, said carbocyclic-nucleosides linked by charged and neutral phosphorous linkages, said carbocyclic-nucleosides linked by non-phosphorous linkages, said β-nucleosides linked by charged and neutral 2'-5' linkages, said β-nucleosides linked by non-phosphorous linkages, said β-nucleosides linked by non-phosphorous linkages, and neutral 2'-5' linkages, and said β-nucleosides linked by non-phosphorous linkages; and

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a second of said regions including said nucleobases linked by nonphosphorous linkages and nucleobases that are attached to phosphate linkages via a non-sugar tethering moiety.

48. (canceled).

49. (new) A method of treating an organism having a disease characterized by the

undesired production of a protein comprising contacting said organism with an

oligonucleotide having a sequence of nucleotides capable of specifically hybridizing to a

strand of ribonucleic acid coding for said protein, where at least one of said nucleotides is

functionalized to increase nuclease resistance of the oligonucleotide, where a plurality of the

nucleotides have a substituent group located thereon to increase binding affinity of the

oligonucleotide to a complementary strand of sequence-specific ribonucleic acid, and where a

plurality of the nucleotides have 2'-deoxy-erythro-pentofuranosyl sugar moieties.

50. (new) The method of claim 49 wherein said substituent group for increasing

binding affinity comprises a 2'-substituent group.

51. (new) The method of claim 49 wherein said substituent group for increasing

binding affinity comprises a 2'-substituent group that is fluoro, C1-C9 alkoxy, C1-C9

aminoalkoxy, allyloxy, imidazolealkoxy or poly(ethylene glycol).

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52. (new) The method of claim 49 wherein each of said nucleotides is a phosphorothioate or phosphorodithioate nucleotide.

53. (new) The method of claim 49 wherein the 3' terminal nucleotide of said oligonucleotide includes a nuclease resistance modifying group on at least one of the 2' or the 3' positions of said nucleotide.

54. (new) The method of claim 49 wherein:

a plurality of said nucleotides bear substituent groups that increases binding affinity of said oligonucleotide to said sequence-specific ribonucleic acid, said substituent-bearing nucleotides being divided into a first nucleotide unit sub-sequence and a second nucleotide unit sub-sequence; and

said plurality of 2'-deoxy-erythro-pentofuranosyl nucleotides is positioned in said sequence of nucleotides between said first nucleotide unit sub-sequence and said second nucleotide unit sub-sequence.

55. (new) The method of claim 49 wherein:

a plurality of said nucleotides bear substituent groups that increase binding affinity of said oligonucleotide to said complementary strand of nucleic acid; and

at least a portion of said substituent-bearing nucleotides are consecutively located at one of the 3' terminus or the 5' terminus of said oligonucleotide.

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56. (new) The method of claim 49 wherein at least five of said nucleotides have 2'-deoxy-erythro-pentofuranosyl sugar moieties, said at least five 2'-deoxy-erythro-pentofuranosyl nucleotides being consecutively located in said sequence of nucleotides.

- 57. (new) The method of claim 49 wherein from one to about eight of said nucleotides bear a substituent group that increases the binding affinity of said oligonucleotide to said complementary strand, said substituent-bearing nucleotides being consecutively located in said sequence of nucleotides.
 - 58. (new) The method of claim 49 wherein:

from one to about eight of said nucleotides bear a substituent group for increasing the binding affinity of said oligonucleotide to said complementary strand, said substituent-bearing nucleotides being consecutively located in said sequence of nucleotides; and

at least five of said nucleotides have 2'-deoxy-erythro-pentofuranosyl sugar moieties, said at least five 2'-deoxy-erythro-pentofuranosyl nucleotides being consecutively located in said sequence of nucleotides.

59. (new) A method of concurrently enhancing hybridization and RNase H activation in an organism comprising contacting the organism with an oligonucleotide having a sequence of nucleotides capable of specifically hybridizing to a sequence-specific ribonucleic acid where at least one of said nucleotides is functionalized to increase nuclease resistance of the oligonucleotide, where a plurality of the nucleotides have a substituent group located thereon to increase binding affinity of the oligonucleotide to a complementary strand

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of sequence-specific ribonucleic acid, and where a plurality of the nucleotides have 2'-deoxyerythro-pentofuranosyl sugar moieties.

60. (new) The method of claim 59 wherein said substituent group for increasing binding affinity comprises a 2'-substituent group.

(new) The method of claim 59 wherein said substituent group for increasing 61. binding affinity comprises a 2'-substituent group that is fluoro, C1-C9 alkoxy, C1-C9 aminoalkoxy, allyloxy, imidazolealkoxy or poly(ethylene glycol).

- 62. (new) The method of claim 59 wherein each of said nucleotides is a phosphorothioate or phosphorodithioate nucleotide.
- 63. (new) The method of claim 59 wherein the 3' terminal nucleotide of said oligonucleotide includes a nuclease resistance modifying group on at least one of the 2' or the 3' positions of said nucleotide.
 - 64. (new) The method of claim 59 wherein:

a plurality of said nucleotides bear substituent groups that increases binding affinity of said oligonucleotide to said sequence-specific ribonucleic acid, said substituent-bearing nucleotides being divided into a first nucleotide unit sub-sequence and a second nucleotide unit sub-sequence; and

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said plurality of 2'-deoxy-erythro-pentofuranosyl nucleotides is positioned in said sequence of nucleotides between said first nucleotide unit sub-sequence and said second nucleotide unit sub-sequence.

65. (new) The method of claim 59 wherein:

a plurality of said nucleotides bear substituent groups that increase binding affinity of said oligonucleotide to said complementary strand of nucleic acid; and

at least a portion of said substituent-bearing nucleotides are consecutively located at one of the 3' terminus or the 5' terminus of said oligonucleotide.

- 66. (new) The method of claim 59 wherein at least five of said nucleotides have 2'-deoxy-erythro-pentofuranosyl sugar moieties, said at least five 2'-deoxy-erythro-pentofuranosyl nucleotides being consecutively located in said sequence of nucleotides.
- 67. (new) The method of claim 59 wherein from one to about eight of said nucleotides bear a substituent group that increases the binding affinity of said oligonucleotide to said complementary strand, said substituent-bearing nucleotides being consecutively located in said sequence of nucleotides.
 - 68. (new) The method of claim 59 wherein:

from one to about eight of said nucleotides bear a substituent group for increasing the binding affinity of said oligonucleotide to said complementary strand, said substituent-bearing nucleotides being consecutively located in said sequence of nucleotides; and

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at least five of said nucleotides have 2'-deoxy-erythro-pentofuranosyl sugar moieties, said at least five 2'-deoxy-erythro-pentofuranosyl nucleotides being consecutively located in said sequence of nucleotides.